COMPARISON OF METOPROLOL TARTRATE MULTIPLE-UNIT LIPID MATRIX SYSTEMS PRODUCED BY DIFFERENT TECHNOLOGIES

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ABSTRACT

The aim of this study was to develop, evaluate and compare extended release mini-matrices based on metoprolol tartrate (MPT) and either glyceryl behenate (GB) or glyceryl palmitostearate (GPS). Mini-matrices were produced by three different techniques: hot melt extrusion, compression of melt granulates and prilling. Hot-melt extrusion and compression of granules obtained from melted material proved to be reliable, robust and reproducible techniques with aim of obtaining extended release matrices. Prilling tended to be susceptible to increased melt viscosity. Direct compression was not applicable for mini-matrix production due to poor powder flow. In general MPT release from all matrices was affected by its loading and the size of the units/particles. Processing of GB - MPT mixtures by different techniques did not lead to different drug release rates and patterns, while in case of GPS differently obtained matrices provided diverse MPT release outcomes. Matrices based on GB tended to have higher porosity compared to ones composed of GPS and thus most of the GB-based formulations showed faster drug delivery. FT-IR analysis revealed no interactions between primary components used for matrix production and Raman mapping outlined uniform MPT distribution throughout the units. DSC and X-ray studies revealed significant changes in the crystallinity of glycerides after storage under room conditions (GPS samples) and at increased temperature (GB and GPS samples), which was correlated to the changes seen in drug release rate and pattern after storage. Media composition in general tended to insignificantly affect GB matrices, while in case of GPS matrices increasing the pH and presence of biorelevant compounds induced faster drug release.

KEYWORDS: mixed glycerides, metoprolol tartrate, hot-melt extrusion, compression, prilling, extended release

1.INTRODUCTION

Extended drug release (ER) provides API delivery in a continuous fashion and subsequently benefits from constant plasma concentration levels and reduced dosing frequency. Formulating product as multiple unit drug delivery system (MDDS) gives advantages such as broad gastro-intestinal distribution, insignificant ‘’all-or-nothing release effect’’, possibility of combining different API’s and different release kinetics in one system and improved swallowing. Combining ER and MDDS platforms is a viable approach towards designing solid dosage forms with added value. [Aulton, 2007; Abdul et al., 2010; Aleksovski et al., 2015a; Aleksovski et al., 2015b; Qui et al., 2009; Randade et al., 2004; Wen and Park, 2010]. Mini-tablets (MT; tablets with d$\leq$ 3mm) are emerging as a promising basis for designing MDDS offering modified drug delivery and also improved swallowing and flexible dosing regarding age/weight/health condition. MT are produced on standard tableting presses equipped with multi-tip punches and multi-bore dies. Production of MT has special requirements with regard to very good powder flow properties, limited particle size and process/press assembly control in terms of obtaining acceptable product and avoiding tooling damage. [Aleksovski et al., 2015b; Klingmann et al., 2013; Klingmann et al., 2015; Spomner et al., 2012; Tomson et al., 2009]) Hot-melt extrusion (HME, combined with uniform extrudate cutting in post processing stage) and prilling are emerging as continuous, robust, simple, less demanding (with regard to flow properties and compressibility) and solvent free techniques for producing of extended release mini-matrices and thus become reliable alternatives to mini-tablet production. HME is a process where powdered material is introduced into a heated barrel equipped with one or two rotating screws which provide melting, mixing, kneading and forcing the material to an end-plate die which determines the shape of the extruded material. Prilling is a technique where a liquid - molten system is forced through a pre-heated narrow nozzle, creating a liquid jet which is broken up into droplets by vibrational energy or periodic nozzle valve movement. These droplets are subsequently cooled down by falling through a tempered cooling tower and gathered as spheres with narrow size distribution. Main drawback of HME and prilling is the requirement of higher processing temperatures, which are in general not suitable for thermo-labile compounds [Ceowley et al., 2007; Lang et al., 2014; Maniruzzaman et al., 2012; Pivette et al., 2012; Repka et al., 2007; Repka et al., 2012; Sequier et

al., 2014; Vervaeck et al., 2013]. Pharmaceutically approved lipids are excipients suitable for production of solid oral dosage forms by melting technologies, due to their biocompatibility, low-toxicity, compatibility with many active compounds, moderate melting temperatures and low cost. High hydrophobicity of some of the lipids is making them suitable for design of extended release systems. However, the main drawback of pharmaceutical lipids is their physical instability, which is correlated with changes of their crystallinity during processing and storage [Reitz and Kleinebudde, 2007a; Rosiaux et al., 2014; Vithani et al., 2013].

The aim of this study was to develop multiple-unit extended-release systems of a highly soluble model drug (metoprolol tartrate, MPT) based on mixed glycerides (glyceryl behenate (GB) and glyceryl palmitostearate (GPS)) as matrix formers and using different production technologies for lipid matrices: prilling (prills - PR), hot-melt extrusion (mini-extrudates - EX), direct compression (directly compressed mini-tablets - DCMT) and compression of melt granulated material (mini-tablets compressed from granules - GMT). All technologies used for production of the matrices are schematically shown in Fig. 1. Experiments were conducted in order to determine how formulation factors (composition, unit/granule size), production technology, dissolution media and storage conditions affected the drug release and the dosage form characteristics in general. Matrices were evaluated by differential scanning calorimetry (DSC), X-ray diffraction, attenuated total reflection Fourier-transform IR spectroscopy (ATR FT-IR), Raman microscopic mapping and micro-computed tomography (μCT) to characterize solid state, drug-lipid interactions, drug distribution and porosity, and to correlate these characteristics with the drug release properties and final product outcome.

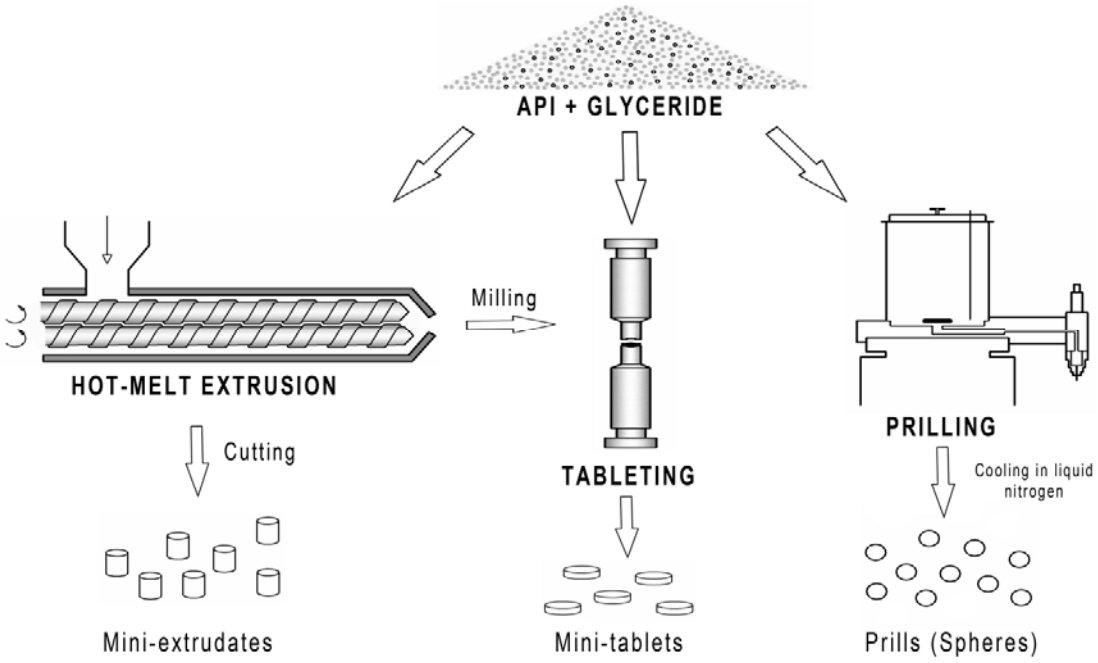

Fig. 1. Schematic presentation of techniques used for production of glyceride matrices.

2. MATERIALS AND METHODS

2.1. MATERIALS

Metoprolol tartarate (MPT) was purchased from Esteve Quimica (Barcelona, Spain). Glyceryl behenate (GB, Compritol® 888 ATO) and glyceryl palmitostearate (GPS, Precirol® ATO 5) were obtained from Gattefosse (St. Priest, France). Magnesium stearate (Mg St) was purchased from ABC Chemicals (Wauthier-Braine, Belgium), colloidal silica dioxide (Aerosil® 200 Pharma) from Evonik (Hanau-Wolfgang, Germany), pancreatin from Sigma Aldrich (USA), sodium taurocholate from Prodotti Chimici e Alimentari (Basaluzzo, Italy) and egg phosphatidylcholine (LIPOID E PC S) from Lipoid (Steinhausen, Switzerland). All other reagents were of analytical grade. The quantitative composition of the formulations processed via the four different techniques is given in Table 1.

Table 1

Compositions in % (m/m) of evaluated mini-matrices based on MPT and mixed glycerides, produced via different technologies.

	Formulations containing GB (%)								
Components	**F1 GB PR**	**F2 GB PR**	**F3 GB PR**	**F1 GB EX**	**F2 GB EX**	**F3 GB EX**	**F1 GB DCMT/GMT**	**F2 GB DCMT/GMT**	**F3 GB DCMT/GMT**
MPT	20	30	40	20	30	40	20	30	40
GB	80	70	60	79.5	69.5	59.5	78.5	68.5	58.5
Aer	/	/	/	0.5	0.5	0.5	0.5	0.5	0.5
Mg st	/	/	/	/	/	/	1	1	1
	Formulations containing GPS (%)								
Components	**F1 GPS PR**	**F2 GPS PR**	**F3 GPS PR**	**F1 GPS EX**	**F2 GPS EX**	**F3 GPS EX**	**F1 GPS DCMT/GMT**	**F2 GPS DCMT/GMT**	**F3 GPS DCMT/GMT**
MPT	20	30	40	20	30	40	20	30	40
GPS	80	70	60	79.5	69.5	59.5	78.5	68.5	58.5
Aer	/	/	/	0.5	0.5	0.5	0.5	0.5	0.5
Mg st	/	/	/	/	/	/	1	1	1

2.2. METHODS

2.2.1. Hot-melt extrusion

Hot-melt extrusion was carried on co-rotating, fully intermeshing, Prism Eurolab 16 mm twin screw extruder (Thermo Fisher Scientific, Karlsruhe, Germany), equipped with a 3mm cylindrical die. The extruder segments (from powder entrance to die) were pre-heated to temperatures (°C) of 77/75/75/75/72/66 and 57/57/57/55/53/50 for mixtures containing glyceryl behenate and glycerol palmitostearate, respectively. Powder mixtures were fed into the extruder by a Brabender Flexwall® loss-in-weight powder feeder (Duisburg, Germany) at a feed rate of 300 g/h and were further transported, mixed and kneaded along the extruder by screw co-rotation at a speed of 40 rpm. Cylindrically shaped extrudates with a diameter of 3mm were obtained and were further manually cut into mini-extrudates (EX) of ≈ 3mm or 5mm in length.

2.2.2. Mini-tablet preparation

Powders aimed to be directly compressed were thoroughly mixed for 15 minutes (with exception of Mg St) in a Paul Schatz principle mixer (Inversina BioEngineering, Wald, Switzerland). Mg St was afterwards added and this mixture was mixed for 1 minute. Mixtures were further evaluated for tap and bulk density and flow through a funnel [PhEur 7, 2007]. Directly compressed mini-tablets (DCMT) were prepared on eccentric tablet press (Korsch, EK 0, Frankfurt, Germany). Punch holders were equipped with single-tipped round, bi-convex punches of 4 mm in diameter. Mini-tablets were prepared using a mean compression force of 3±0.3 kN at tableting speed of 20 tablets/min. Each mini-tablet weighed approximately 30 mg. Mini-tablets (GMT) were prepared from milled extrudates (Coffee grinder - AR100G31, Moulinex, France; milling time: 4 sequences of 3 s with 5 s interruption). Obtained powders were subsequently treated as the ones intended for direct compression. In the second part of the study GMT samples were prepared by sieved fractions with particle size of 0.150 mm ≤ d ≤ 0.250 mm (GMT-S) or 0.500 mm ≤ d ≤ 0.750 mm (GMT-L).

2.2.3. Prilling

Prilling was performed with a custom-designed device, made by Peira (Turnhout, Belgium) as described by Vervaeck et al [Vervaeck et al., 2013]. In order to obtain melts with suitable viscosity, mixed glycerides were first melted and heated at 100°C inside the container of the prilling machine. Afterwards the active compound was slowly added while continuously mixing using a magnetic stirrer. Droplet generation was started after complete dispersion of the drug in the molten glyceride while continuous stirring was maintained. By applying a pneumatic pressure (0.8 Bar) in the headspace above the suspension, the mixture was fed towards the thermostated nozzle (at 99 °C) equipped with a valve and a capillary (inner diameter: 0.33 mm). To obtain droplets of appropriate size a periodic droplet formation time (i.e. period during which the inlet valve is opened) of 0.07 s was applied. Droplets were then quench cooled in liquid nitrogen in order to solidify and form spherical particles – prills (PR). These process parameters were applied to formulations with 20 % MPT, while at higher content of the drug the suspension was too viscous to find appropriate process parameters for the droplet formation.

2.2.4. Drug release studies

In vitro dissolution was performed using USP dissolution apparatus 1. The dissolution system was coupled with an automatic sampling station (Vankel, New Jersey, USA). A number of matrices, corresponding to 30 mg MPT, was placed into baskets, and demineralized water, 0.1 N HCl (pH 1) or phosphate buffer [PhEur 7, 2007] (pH 6.8) in amount of 900 mL were used as dissolution media. Basket rotational speed was set to 100 rpm and the temperature of the dissolution medium was maintained at 37 °C. Samples of 5 ml were withdrawn after 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 h and then analyzed spectrophotometrically at λ=222 nm using a double beam spectrophotometer (UV-1650PC, Shimadzu, Tokyo, Japan). Drug concentrations were obtained from a calibration curve constructed between 0 and 33µg/ml. Each dissolution experiment was performed in triplicate.

In vitro dissolution was additionally performed in 900 mL biorelevant media (FESSIF; pH 6.5), prepared as per Marques [Marques, 2004] with addition of pancreatin and $CaCl_2$ as per Witzleb et al [Witzleb et al., 2012]. The above mentioned dissolution test parameters were kept and each

experiment was done in triplicate. Results obtained in FESSIF media were compared to those obtained in blank FESSIF (without pancreatin, sodium taurocholate, lechitine and $CaCl_2$; pH 6.5). Samples of 5 ml were withdrawn after 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 h, diluted with methanol in a 1:3 ratio, filtered through 0.45µm regenerated cellulose (RC) filter and analyzed by HPLC method (Agilent 1100 series, USA), adapted from Leigh et al [Leigh et al., 2013]. The method was based on a gradient flow of a mobile phase A (0.1% H_3PO_4 in water) and mobile phase B (acetonitrile) at flow rate of 1 ml/min on a SunFire C18 column, 50×4.6 mm, 3.5 µm, (Waters, Ireland), equipped with a pre-column at 40 °C. Injection volume was 60 µl, detection was performed at 222 nm with a total run time of 8.5 min. The drug concentrations in samples were calculated from a corresponding calibration curve obtained from MPT standards spiked into each dissolution media in a concentration range between 0 and 33 µg/ml. Each experiment was performed in triplicate.

In order to compare how does the production technique or unit/granule size or the dissolution medium affect the drug release a similarity factor (*f2)* was calculated using the following equation (Eq. (1)):

$$f_2 = 50 \log\left(\frac{100}{\sqrt{1+\frac{\sum_{i=1}^{n}(T_i-R_i)}{n}}}\right) \quad (1)$$

where n is number of sampling points; R_i is mean % of released drug amount from a reference product at time (t), while T_i is mean % of released drug amount from the test product at the same time (t). f_2 values ≥50 point to in vitro similar drug release profiles.

2.2.5. Storage stability study

Selected formulations were placed into a strong vapour barrier bags consisting of three-layer foil (PET/aluminium/PE), which were heat-sealed and placed into a climatic chamber. Products were stored for two months at 25°C/65% RH (room conditions) and 40 °C/75% RH (accelerated conditions), mimicking different climate conditions. Samples were then evaluated for drug/lipid

solid state properties (DSC, XRPD, Raman mapping and FT-IR) and drug release in demineralized water.

2.2.6. Differential scanning calorimetry (DSC)

The thermal properties of the pure substances, physical mixtures (PM) and selected formulations were evaluated using calibrated differential scanning calorimeter Q2000 (TA Instruments, New Castle, USA) equipped with a refrigerated cooling system. Samples (5-10 mg) were run in Tzero pans (TA Instruments, New Castle, USA) with an underlying heating rate of 10 °C/min. Dry nitrogen was applied as a purging gas through the DSC cell at a flow rate of 50 ml/min. DSC data were analyzed using the Universal Analysis software (TA Instruments). Melting enthalpies were determined in the total heat flow signal.

2.2.7. X-ray diffraction

X-ray diffraction was performed on pure compounds, their physical mixtures and selected final formulations to evaluate the constituent's crystallinity. Measurements were performed by step scan mode (step size = 0.02°, counting time = 1 s/step) with a D5000 Cu Kα diffractor (λ = 1.54 Å) (Siemens, Karlsruhe, Germany) at 40 mV voltage in the angular range of $10° < 2\theta < 70°$.

2.2.8. Attenuated total reflection Fourier-transform infrared (ATR FT-IR) spectroscopy

ATR FT-IR spectroscopy was conducted on the pure compounds, physical mixtures, and selected final products in terms of identification of possible interactions between the drug and mixed glycerides, occurring during the different production processes. Spectra were recorded using ATR FT-IR spectrometer (Thermo Fisher Scientific, Nicolet iS5 ATR FT-IR spectrometer). A diamond ATR crystal was pressed against the samples. Each spectrum was collected in the 4000 – 550 cm^{-1} range with a resolution of 2 cm^{-1} and averaged over 50 scans.

2.2.9. Raman Spectroscopy

The distribution of MPT in cross-sections of extrudates, prills and mini-tablets was evaluated by Raman microscopic mapping. Raman spectra were collected with a Raman Rxn1 Microprobe (Kaiser Optical Systems, Ann Arbor, MI, USA) equipped with an air-cooled CCD detector and a

785 nm Invictus NIR diode laser. Each sample surface was scanned by a 10x - long working distance objective lens (spot size 50 µm) in area mapping mode using a step size of 50 µm in both the x (18 points) and y (12 points) direction, resulting in a total of 216 spectra or a covered area of 850 x 550 µm for each mapping segment. Raman shift spectra were collected over the 0 - 1800 cm^{1} range with a resolution of 4 cm^{-1} and an exposure time of 4 s, using a laser power of 400 mW. Data collection and data transfer were automated using HoloGRAMS™ data collection software (version 2.3.5, Kaiser Optical Systems), the HoloMAP™ data analysis software (version 2.3.5, Kaiser Optical Systems) and Matlab software (version 7.1, The MathWorks, Natick, MA, USA).

Each mapping was analyzed using multivariate curve resolution (MCR) approach to determine the composition homogeneity of the samples. Therefore for each mapping segment all 216 spectra were introduced in a data matrix. Because each sample consisted of two components, 2-factor MCR was applied. Additionally, both a spectrum of pure MPT and either GB or GPS were added to this data matrix. The spectral range was narrowed until 1140-1320 cm^{-1}, containing specific peaks for both components. First, all spectra were baseline corrected using Pearson's method and subsequently they were normalized, obtaining data matrix D containing the preprocessed spectra. MCR aims to obtain a clear description of the individual contribution of each pure component in the area from the overall measured variation in D [De Beer et al., 2009]. Hence, all collected spectra in the area are considered as the result of the additive contribution of all pure components involved in the area. Therefore, MCR decomposes D into the contributions linked to each of the pure components in the system, described by the equation 2:

$$D = CS + E \quad (2)$$

where C and S represent the concentration profiles and spectra, respectively. E is the error matrix, which is the residual variation of the dataset that is not related to any chemical contribution. Next, the working procedure of the resolution method started with the initial estimation of C and S and continued by optimizing iteratively the concentration and response profiles using the available information about the system. The introduction of this information was carried out through the implementation of constraints. Constraints are mathematical or

chemical properties systematically fulfilled by the whole system or by some of its pure contributions. The constraint used for this study was the default assumption of non-negativity; that is, the data were decomposed as non-negative concentration times non-negative spectra [De Juan and Tauler, 2003].

2.2.10. Porosity assessment by Micro Computed Tomography (µCT)

Local planar representations of the sample porosity were visualized by a SkyScan 1172 high-resolution µCT apparatus (Bruker, Belgium), equipped with a Hamamatsu 1.3 megapixel camera. Pixel size of 5.03 µm with aspect ratio of 1 was obtained in the pictures. The object-to-X-ray source distance was 48 mm and the object-to-sensor distance was 216 mm. The rotation of the sample was performed for 180° and the rotation step was 0.5°. 50 slices, each representing sample depth of 5.03 µm (2D pictures), were collected into a stack by using ImageJ software (National Institute of Health, Bethesda, USA). 4 stacks of overall 1 mm sample depth were analyzed. Every stack was thresholded to separate the void space of pores from the solid material. A threshold value was used, which isolated the black pixels belonging to the pores and thus gave an area of the void spaces. Stack overall pore volume was determined as follows: the black pixels obtained on the stack slices were summed and multiplied with the thickness of the slice. Sample's total area and volume for individual stack was determined by drawing a polygon around the object perimeter and then multiplying total object area with stack depth. The porosity of the sample stack was then calculated as the ratio of the stack overall pore volume and object total volume for corresponding stack. Porosity of the sample is reported as average and standard deviation of porosities obtained for four subsequent stacks.

3. RESULTS AND DISCUSSION

3.1 Effect of the production process type and mixed glyceride-to-drug ratios on the material processing and drug release pattern

HME and tableting of milled extrudates tended to be the most reliable and robust techniques in terms of producing extended release mini-matrices in all drug-glyceride ratios. On the other hand direct compression of powder mixtures was seen as non-suitable technique due to inadequate powder flow properties of the DC formulations (both F1 GB and GPS DCMT did not flow through the funnel orifice and had Carr's index values higher than 33) and was hence eliminated from further study. During prilling only formulations containing the lowest concentration of MPT (20 %) were able to be processed into round spheres which prolonged MPT delivery. By adding the drug into the molten lipid a mixture with high viscosity was obtained due to the fact that MPT is mainly non-soluble in both glycerides. Increasing the drug content to 30 % or 40 % gave viscous molten masses which tended to block the needle of the prilling machine. Prilling of mixtures containing mixed glycerides (80%) and MPT (20%) formed fragile spheres, which may be due to the crack formation inside the core upon quench cooling seen also by Vervaeck et al. [Vervaeck et al., 2015] for prills containing behenic acid and MPT. Subsequently prill manipulation was done with caution in terms of avoiding their breakage.

The chosen mixed glycerides are highly hydrophobic and their incorporation inside a formulation may strongly affect the drug release rate. Decreasing the glyceride content from 80% to 60 % resulted in faster drug release in all EX (Fig. 2A and 2B) and GMT formulations (supplementary material – Fig. S1). EX, GMT and PR containing 20% drug (F1) were selected for further evaluation since they provided the slowest and almost complete drug delivery over 24 hours. As all characterizations were performed at this specific drug content, F1 designation is omitted from sample labels from this point on.

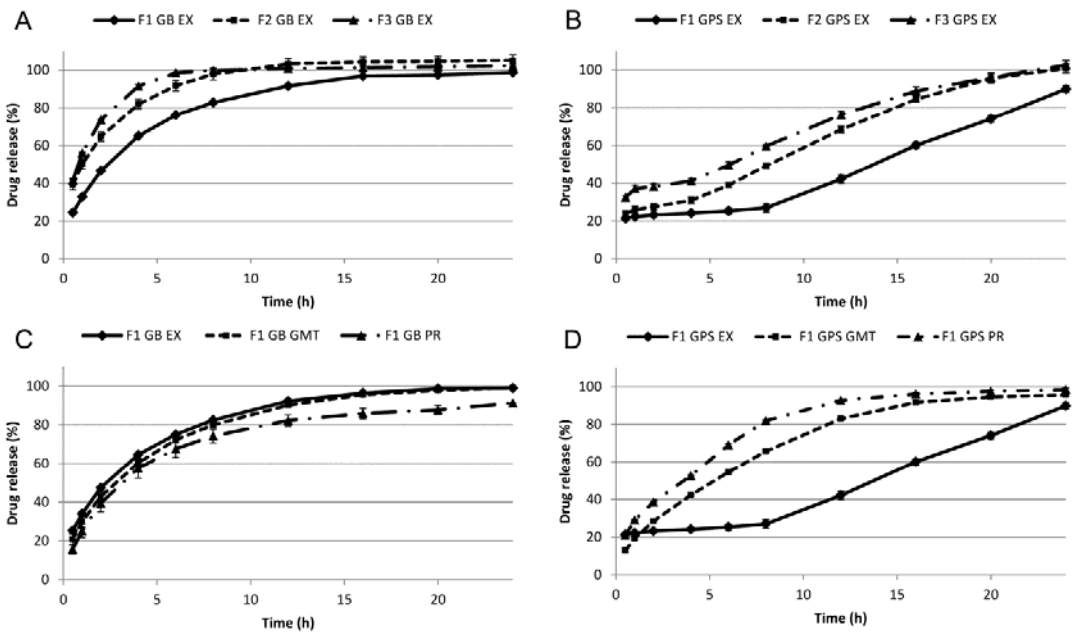

Fig. 2. (A) Drug release in purified water from GB EX containing 20%; 30% or 40% MPT; (B) drug release in purified water from GPS EX containing 20%; 30% or 40% MPT; (C) drug release from GB matrices containing 20% MPT produced via different technologies; (D) drug release from GPS matrices containing 20% MPT produced via different technologies.

MPT is classified as BCS class I drug with pH independent solubility exceeding 1000 mg/ml in purified water [Klein and Dressman, 2006; Santa Cruz Biotech, 2015]. Subsequently MPT solubility was not seen as limiting factor for the doses of 30 mg considered in this study. The production process did not result in significantly different drug release patterns (in purified water) in case of GB matrices even though they have different size and shape (Table 2). All F1 GB products (Fig. 2C) gave square root of time MPT release during the dissolution testing (GB PR (R^2=0.987, RMSD=2.4%); GB GMT (R^2=0.995, RMSD=1.5%); GB EX (R^2=0.984, RMSD=2.3%)). On the other side GPS as lipid showed more diverse drug delivery patterns when processed by different technologies (Fig. 2D, Table 2): GPS extrusion gave a sigmoidal drug delivery pattern with initial burst release in the first half hour followed by slower drug release up to 8 hours and faster drug release during remaining dissolution time. GPS-based GMT and PR again gave square

root of time release pattern (GPS GMT (R^2=0.982, RMSD=3.1%); GPS PR (R^2=0.992, RMSD=2.0%)) without the lag time observed for EX samples.

Table 2

In-vitro similarity of dissolution profiles (similarity factor - f_2) of chosen formulations produced by different technologies or tested/stored at different conditions.

Comparison	Similarity factor (f_2)
Influence of production technology	
GB EX vs GB GMT (purified water)	72
GB EX vs GB PR (purified water)	50
GB GMT vs GB PR (purified water)	56
GPS EX vs GPS GMT (purified water)	28
GPS EX vs GPS PR (purified water)	22
GPS GMT vs GPS PR (purified water)	48
Influence of granule size	
GB GMT S vs GB GMT L (purified water)	56
GPS GMT S vs GPS GMT L (purified water)	78
Influence of medium composition	
GB GMT (0.1 M HCl vs phosphate buffer pH 6.8)	72
GPS GMT (0.1 M HCl vs phosphate buffer pH 6.8)	48
GB PR (FESSIF vs Blank FESSIF)	51
GPS EX (FESSIF vs Blank FESSIF)	44
Influence of storage conditions	
GB GMT fresh vs 25°/65% (purified water)	79

GB GMT fresh vs 40°/75% (purified water)	20
GPS EX fresh vs 25°/65% (purified water)	34
GPS EX fresh vs 40°/75% (purified water)	35

Sigmoidal drug delivery from GPS EX may be linked to the so-called ''wall depletion'' effect [Reitz et al., 2008]. Wall depletion occurs due to shearing profile at die wall during extrusion which induces drug migration towards extrudate core leaving thin layer rich in lipid on the extrudate surface. This thin lipid layer acts as a diffusion barrier, limiting water penetration inside the matrix. Based on this mechanism of drug delivery from GPS EX can be further explained. The initial burst release is probably due to dissolving of MPT fraction located at the extrudate surface and especially due to API leach from the pores located on the surface of extrudate cut ends. When superficial drug is released, the thin lipid layer positioned at extrudate lateral sides limits water penetration and promotes drug release mainly from the pores extending from both cut ends (lateral surface : cut ends = 3 : 1). The change in MPT release rate from 8 h onwards could be connected with longitudinal cracking of the extrudate during dissolution, which was observed after the test and only in this type of matrix (supplementary material – Fig. S2). This phenomenon was also mentioned in a study performed by Reitz and Kleinebudde for GPS: theophylline EX (50 % : 50 %) [Reitz and Kleinebudde, 2007b]. Additional milling of the extrudates into granules in case of GPS GMT eliminated the barrier effect, exposing more API in contact with the dissolution media as stated by Reitz et al. (2008). From the obtained dissolution results (Fig. 2D) it could be concluded that GPS prilling does not yield a product with a lipid-enriched surface.

When comparing drug release in purified water of the same types of dosage form formulated with different lipids (Fig. 2C and 2D) it could be seen that GPS EX provided a slower and completely different drug delivery pattern in comparison to GB EX. Release from GPS GMT was also slower compared to GB GMT. Dissolution results of prills based on different glycerides were of interchangeable nature.

Porosity determination (Fig. 3, Table 3) may explain the differences in the dissolution behavior of the same type of matrices based on different glycerides.

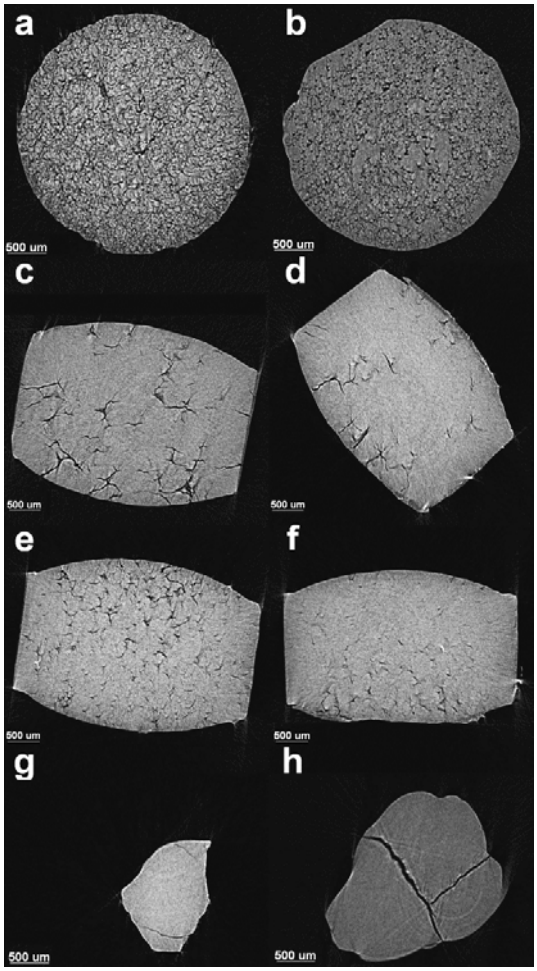

Fig. 3. Representative µCT images (slices) of glyceride matrices obtained by different technologies (A) GB EX; (B) GPS EX; (C) GB GMT L; (D) GPS GMT L; (E) GB GMT S; (F) GPS GMT S; (G) GB PR (fragment); (H) GPS PR. GMT L were compressed from larger granules (0.500 ≤ d ≤ 0.750 mm) while GMT S were compressed from smaller granules (0.150 ≤ d ≤ 0.250 mm)

Table 3

Porosities of matrices based on different glyceride and produced by different technologies (calculated from the reconstructed µCT images)

Type of product	Glyceryl behenate		Glyceryl palmitostearate	
	Porosity (%)	SD	Porosity (%)	SD
EX	5.2	0.3	3.6	0.1
GMT L (mm) (0.500≤d≤0.750)	1.5	0.4	0.9	0.2
GMT S (mm) (0.150≤d≤ 0.250)	0.7	0.2	0.4	0.1
PR	0.8	0.6	1.0	0.8

The type of the glyceride used influenced the porosity of the units in case of extrusion and compression (EX and GMT). Independently of the preparation method, samples based on GB showed a higher porosity compared to the samples produced with GPS (Table 3). These results are in accordance with the ones obtained for drug release in purified water, wherein GB EX and GB GMT had higher drug delivery rate compared to the same units based on GPS. The number of pores and overall porosity in GB EX samples (Fig. 3a and Table 3) might be sufficient to overcome the lipid layer barrier effect, as one would still expect that wall depletion would happen also during extrusion of GB. Additionally analyzing the μCT images of the extrudate edges revealed higher surface porosity of GB EX compared to GPS EX which shows denser surface with less pores (supplementary material – Fig. S3). The variability of the prill's porosity is high which may be due to the large cracks formed inside the units. The variable porosity, crack appearance and possible differences in shape and size of prills due to sphere fragility may lead to the interchangeable nature of drug release from this type of product and thus cause inability to make a distinctive conclusion regarding release properties. Apart from the glyceride type, also the production process tended to provide samples with different qualitative pore structure, pore distribution (Fig. 3) and overall porosity (Table 3). The extruded samples had the highest porosity with a loose texture observed throughout the matrix. GB GMT and GPS GMT have denser texture compared to EX with bigger pores, localized mainly at one of the tablet convex surfaces. The prilled samples

have similar optical density as the tablets, and as already mentioned they contain only few but large cracks located inside the matrix.

Investigating of drug-glyceride interactions was seen as reasonable step in understanding the dissolution results of the mini-matrices involved in this research paper. ATR FT-IR analysis of pure compounds revealed specific peaks for metoprolol tartrate (Fig. 4A) appearing at 1583 cm^{-1} and 1513 cm^{-1} (referring to $\nu_{C=C}$ stretching vibration of the aromatic ring), 1249 cm^{-1} (δ_{β}in-plane O-H deformation), 1109 cm^{-1} (ν_{C-OH} streaching) and 819 cm^{-1} (δ_{γ} out of plane aromatic C-H vibration), which were in accordance with the results obtained by Vervaeck et al. [Vervaeck et al., 2013]. GB (Fig. 4B) and GPS (Fig. 4C) demonstrated almost identical FT-IR spectra with the most specific peaks appearing at 2915 cm^{-1} and 2848 cm^{-1} (C-H valent stretching vibrations) and 1736 cm^{-1} (C=O carbonyl group valent vibration). Specific API and glyceride peaks were also seen in their physical mixtures. Evaluating FT-IR patterns of GB EX (Fig. 4E) and GPS EX (Fig. 4G) and comparing them with the spectra of MPT-GB or MPT-GPS physical mixtures (20 : 80, Fig. 4D for MPT:GB and Fig. 4F for MPT:GPS), respectively did not demonstrate any discernible difference between the spectra of the final products and the ones of the physical mixtures. Similar results were obtained for GB or GPS GMT and PR (supplementary material – Fig. S4). This suggested that no significant chemical interactions occurred between the two compounds inside the matrix regardless of the production process and thus minimized the possibility that they could influence the drug release.

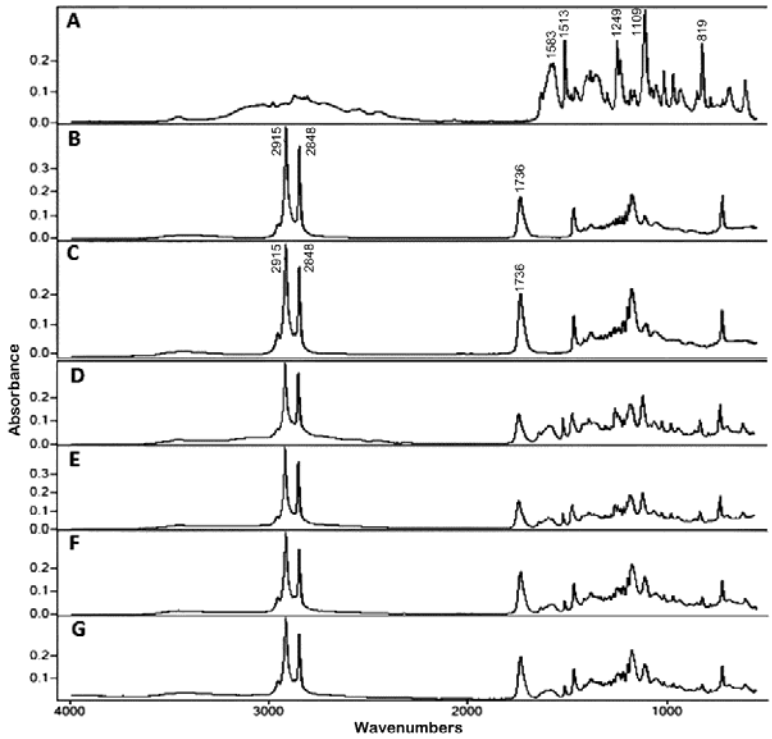

Fig. 4. Drug-glyceride interactions in extrudates based either on GB or GPS. FT-IR spectra of (A)pure MPT; (B) pure GB; (C) pure GPS; (D) MPT-GB physical mixture; (E) GB EX; (F) MPT-GPS physical mixture; (G) GPS EX.

Drug distribution throughout the matrix may be also an important factor influencing drug dissolution of differently produced samples. The homogeneity of the MPT distribution in the samples was evaluated by Raman microscopic mapping. The relative contribution of both components (MPT and glyceride) to each Raman spectrum of the mapping of GB based matrices, comprising MPT is plotted in Fig. 5. Here, straight lines were obtained in the contribution plot which indicated that both components had an equal contribution to all 216 spectra across the mapped area. This spatially equal contribution indicated that MPT was homogenously distributed in the glyceride matrix. Only the last two spectra in the contribution plots deviated from the straight line, because they represented the spectra of the pure components which were added for the data analysis. Similar results were obtained also for GPS-based products and all products after storage (supplementary material – Fig. S5, S6 and S7). Edges of GPS EX sample contrary to expectation did not reveal drug inhomogeneity, which could be due to relatively coarse

resolution of Raman mapping method (i.e. 50 μm). Furthermore Reitz et al. (2008) stated that wall depletion is not considered as inhomogenous drug distribution through the matrix of GPS extrudate [Reitz et al., 2008]. The above mentioned results not only point out that homogenous drug distribution was achieved throughout all evaluated matrices but also that distribution was not dependent on glyceride type nor on production process. Consequently drug distribution could be excluded as further possible factor affecting drug dissolution pattern and rate.

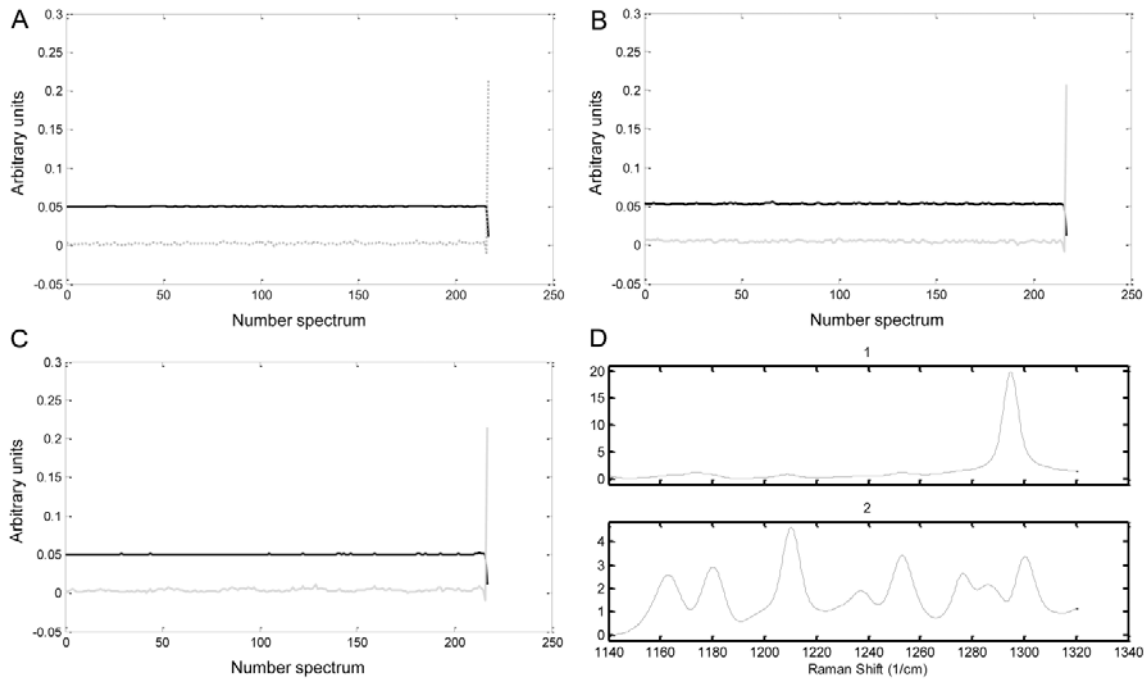

Fig. 5. Drug distribution in GB matrices obtained by different technologies. Contribution plot: Black line: contribution GB; Gray line: contribution MPT, (A) GB EX (B) GB GMT, (C) GB PR, (D) individual signal of GB (1) and individual signal of MPT (2).

Solid state behavior of the matrices was studied using DSC and XRPD. In preliminary DSC experiments all pure compounds showed sharp melting peaks outlining their crystalline nature (Fig. 6A). Mixing MPT with pure glycerides in physical mixtures slightly changed the thermal behavior of the drug since its melting peak shifted towards lower temperatures and gave lower enthalpy value (MPT-GB PM – 15.47 J/g; MPT-GPS PM – 12.55 J/g) compared the theoretically calculated (20% of the enthalpy of pure MPT) MPT enthalpy value of 21.38 J/g. These findings are

suggesting MPT's partial solubilisation inside the molten lipid (28% solubilized MPT in GB and 41 % solubilized MPT in GPS) during DSC analysis. When GB EX and GB GMT (Fig. 6B-2 and 6B-3) were compared to the physical mixture GB-MPT (Fig. 6B-1), matrices showed higher melting enthalpies of GB (EX - 107.3 J/g and GMT –103.4 J/g) compared to physical mixture (92.01 J/g), which may suggest that the glyceride underwent change in its crystalinity after extrusion and also possibly by subsequent tableting. This was not the case with GB PR, which demonstrated similar enthalpy values (92.83 J/g) as the GB in physical mixture (Fig. 6B-4). The differences of the melting peak characteristics between GB products may be connected to the differences of production processes. Namely in case of EX and GMT, employed extrusion was started at 77-75°C which is very close to the melting point of the glyceride. These temperatures enable part of the lipid to remain solid and unchanged during extrusion as already reported by Reitz and Kleinebudde for GPS and glyceryl trymyristate [Reitz and Kleinebudde, 2007a]. On the other hand in prilling mixture processing is conducted at 100°C which induced complete glyceride melting. Additionally extrusion is a more gradual process concerning product temperature drop compared to prilling where the spheres are quickly solidified inside liquid nitrogen. Similar trends as reported for GB were observed in the GPS matrices thermograms (Fig. 6C). However, all three GPS products demonstrated higher enthalpy values and melting peak maximum values of GPS compared to the GPS-MPT physical mixture. GPS EX (Fig. 6C-2) and GMT (Fig. 6C-3) had similar thermal profile with a shouldered glyceride peak, while this shoulder did not appear in the GPS peak of prilled sample (Fig. 6C-4). This shoulder appearance in EX and GMT could be due to the partial melting of lipid and subsequent recrystallization of the molten mass by cooling as described previously by Reitz and Kleinebudde [Reitz and Kleinebudde, 2007a]. As for MPT in fresh matrices its melting peak was even more shifted towards lower temperatures values compared to the one seen in both physical mixtures, which may suggest higher MPT and glyceride particle contact surface values in real process (extrusion with(out) milling and tableting, prilling) compared to the simulated one (heat/cool cycle inside DSC). Additionally, in case of GB matrices even lower enthalpy values (figure 6B) compared to the PM were noted for MPT, suggesting even higher degree of drug solubilization inside the molten glyceride. Based on this the solubilized portion of MPT in GB EX, GMT and PR was 54%, 55% and 61 %, respectively. In case of GPS matrices and PM similar

outcomes were seen, with EX, GMT and PR showing extent of drug solubilisation in amount of 39%, 47% and 64%, respectively. As could be noted prilling as a process is leading to highest degree of MPT solubilization when either GB or GPS is used.

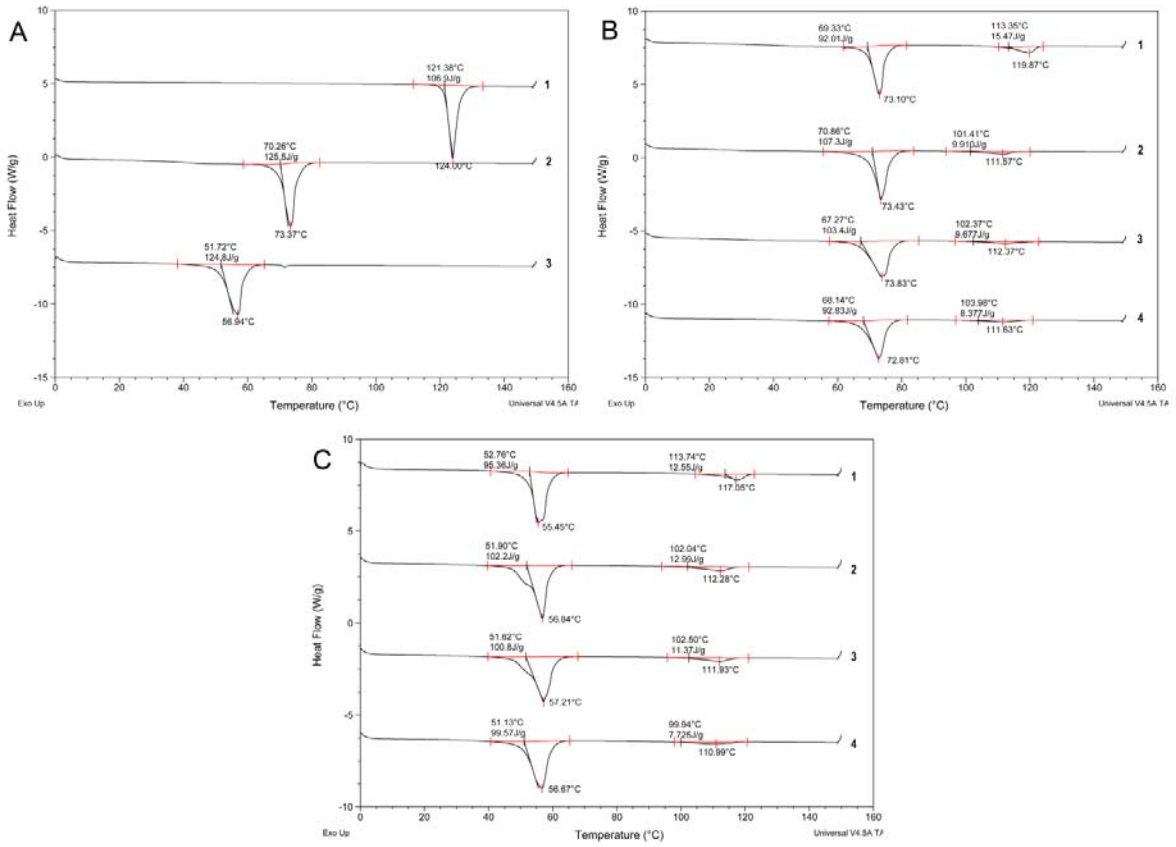

Fig. 6. Thermal behaviour of primary compounds and freshly produced matrices. Thermograms of (A) pure compounds - (1) pure MPT, (2) pure GB, (3) pure GPS; (B) GB based matrices – (1) GB-MPT PM, (2) GB EX, (3) GB GMT, (4) GB PR; (C) GPS based matrices – (1) GPS-MPT PM, (2) GPS EX, (3) GPS GMT, (4) GPS PR; PM denotes physical mixture.

X-ray diffraction patterns of pure compounds confirmed their crystallinity already demonstrated by the DSC results (Fig. 7). MPT showed significant peaks for 2ϑ at 10.6°; 15.8°; 19.4°, 20.4°, 23.1° and 24.5° (Fig. 7A). Pure GB (Fig. 7B) showed only 2 significant crystal peaks for 2ϑ at 21.3° and 23.5° while pure GPS (Fig. 7G) showed only one crystaline peak for 2ϑ at 21.2°. X-ray diffractograms of GB (Fig. 7D-7F) and GPS fresh matrices (Fig. 7I-7K) showed slight difference with

the patterns of the raw materials (physical mixtures) and between themselves which could be connected to the difference seen already in DSC measurements. One difference between GB products and the physical mixture GB-MPT (Fig. 7C) was seen in the absence of splitted peaks at 23.2° and 23.5° in the first ones which as stated by some literature sources may be due to decreased sharpness of the second GB peak (23.5°) after thermal processing [Hamdani et al., 2003; Souto et al., 2006]. Similar results and trends were seen also in case of GPS where the glyceride diffraction pattern in physical mixture (Fig. 7H) was broader and more pronounced compared to the finished products. When comparing the X-ray patterns of the three types of matrices (in case of GB or GPS), no significant differences could be seen between themselves except a decrease of pattern intensity in the prilled sample diffractograms. The drop in intensity may suggest reduced crystallinity of the formulation compounds after prilling and may correspond to the thermal differences seen between EX and GMT on one side and PR on other side. As for the drug compound, MPT could appear in two polymorphic forms- form I and form II which differ in the mechanical properties but not in the bioavailability [Singhal and Curatolo, 2004; Snider et al, 2004]. Significant x-ray MPT peaks at their native places (2ϑ at 10.6; 15.8; 19.4), observed before and after processing, suggests that transformation of the drug from one to another polymorphic form did not occur.

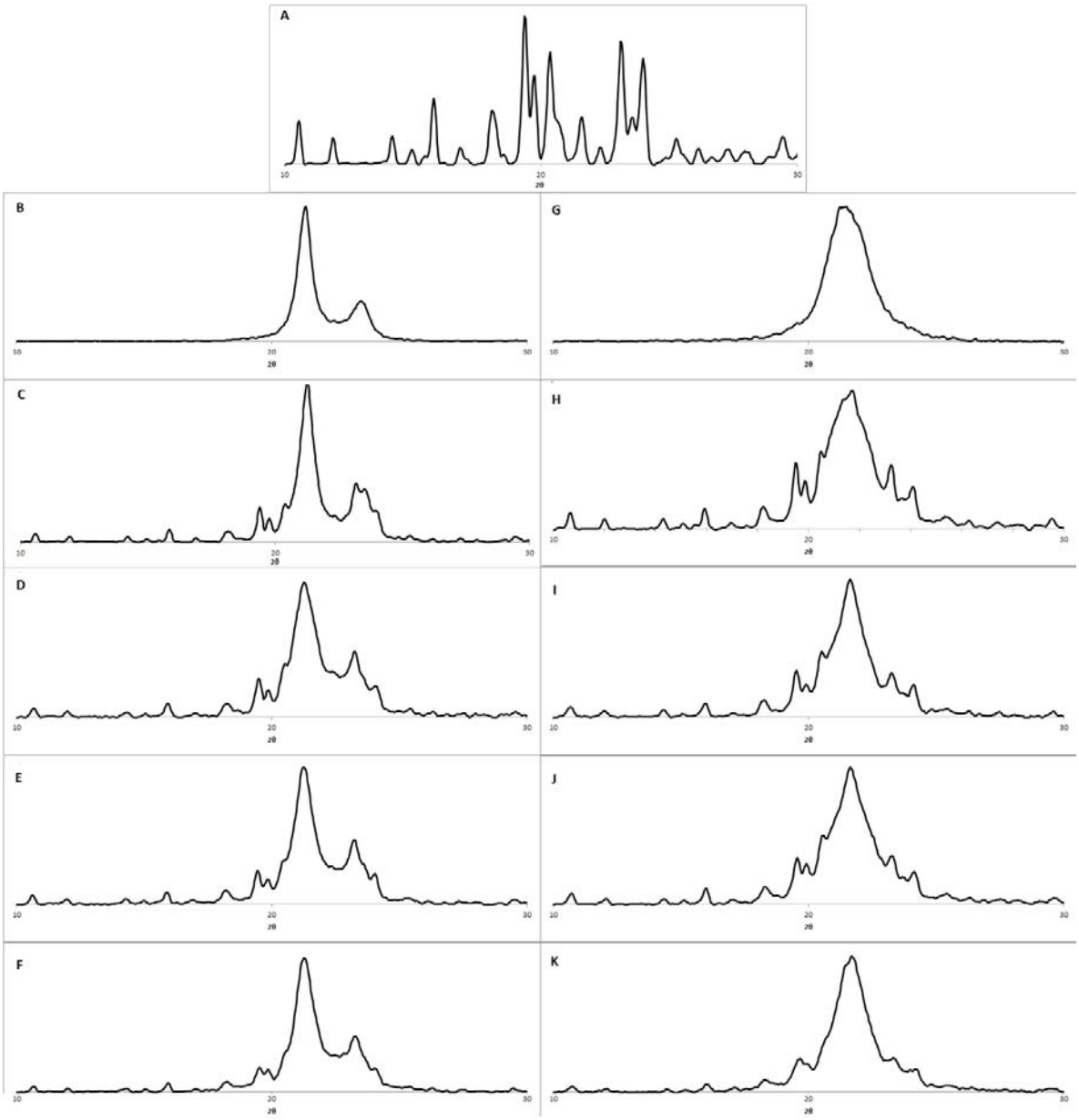

Fig. 7. Crystal nature of primary compounds and freshly produced matrices. X-ray diffractograms of (A) pure MPT; (B) pure GB; (C) pure GPS; (D) MPT-GB PM; (E) GB EX; (F) GB GMT; (G) GB PR; (H) MPT-GPS PM; (I) GPS EX; (J) GPS GMT; (K) GPS PR.

All these findings indicate that the production process may influence the crystal character of glycerides and MPT, however since the results are pointing just indicative (subtle) differences, it is difficult to draw main conclusions on how the solid state character of the products immediately

after the production affected the drug release. Regardless of MPT solid state we can understand prepared mini-matrices (invariant of used technology) as highly soluble drug embedded, hydrophobic matrix systems, that do not undergo significant swelling nor erosion during dissolution and thus drug release is mainly governed by diffusion of the dispersed active compound from the pores of the system. Prepared matrices represent low initial porosity systems, which pores are mainly formed during dissolution and diffusion of embedded drug. This assumption can be further substantiated with the fact that prepared mini-matrices exhibited square root of time release.

3.2 Effect of the matrix size and constituent particle size on the release pattern

By increasing the size of the extrudates (from 3mm to 5mm) and the prills (from 1.4mm to 2mm) a lower MPT release rate was noted when either GB or GPS was used as matrix former (supplementary material – Fig. S8). This is mainly due to the reduced contact surface of units and also due to their increased diffusion pathway. Concerning the influence of granule size on the drug release, in the case of GB, GMT compressed from smaller particles (GB GMT S; 0.15 mm ≤d ≤0.25 mm) tended to release the drug slower than the GMT compressed from larger granules (GB GMT L; 0.5 mm ≤d ≤ 0.75mm), as shown in Fig. 8A, but however the release profiles of the two types of mini-tablets were still in-vitro similar (Table 2). These results are correlated with the µCT measurements where the GB GMT S sample had a lower overall porosity and smaller pores compared to GB GMT L (Table 3 and Fig. 3C and Fig. 3E). In case of GPS GMT compressed from larger (GPS GMT L) or smaller granules (GPS GMT S) no significant difference in the drug release profile was observed (Fig. 8B, Table 2). The lower overall porosity of GPS GMT samples in comparison with GB GMT samples (Table 3) suggests better compactibility of GPS granules (both small and large) and thus less difference in unit porosity and hence in the MPT release pattern.

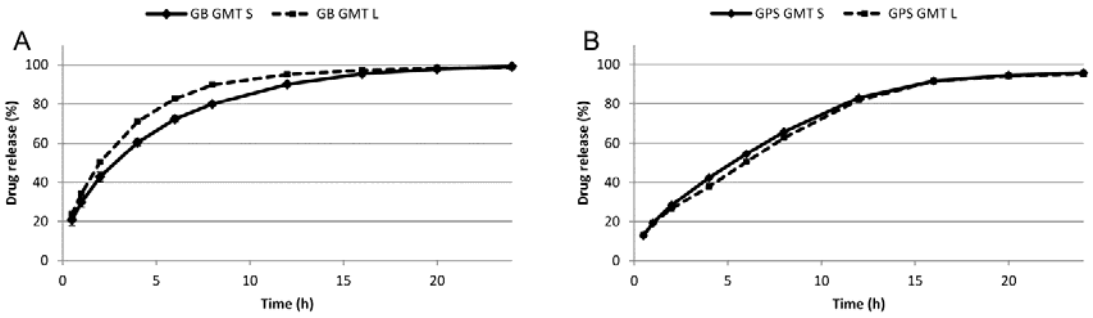

Fig. 8. Influence of granule size on drug release from (A) GB GMT; (B) GPS GMT based either on smaller (0.15 mm ≤d ≤0.25 mm; GMT S) or larger (0.5 mm ≤d ≤ 0.75mm; GMT L) granular fraction (dissolution medium: purified water).

3.3 Effect of storage conditions on the drug release pattern

Storing water vapour protected samples at room conditions (25°C/65%) and at elevated temperature and humidity (40°C/75%) for 2 months in general affected the dissolution pattern of the matrices. In case of GB GMT (Fig. 9A) storage at room temperature did not induce significant changes of the drug delivery rate compared to the freshly prepared samples, while storing the samples at higher temperature resulted in lower drug release compared to the freshly prepared samples (Table 2), as seen also by Witzleb et al. (2012). Similar results were also obtained for GB EX and GB PR (supplementary material – Fig. S9) although the reduction in the drug release rate after storing at increased temperature was less compared to GB GMT.

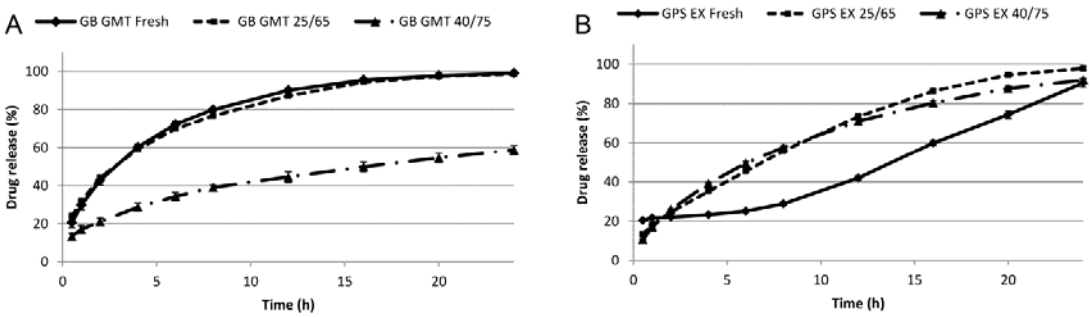

Fig. 9. Influence of storage under room temperature conditions or conditions of elevated temperature on the drug release from (A) GB GMT and (B) GPS EX (dissolution medium: purified water).

The lower drug release rate after storage of GB products at accelerated condition may be connected to changes in the crystallinity of the glyceride: an increase in glyceride melting enthalpy in samples stored for 2 month at accelerated conditions (Fig. 10A for GB GMT). X-ray pattern of stored GB GMT remained unchanged (Fig. 10B), which was also seen by Hamdani et al. (2003). Similar X-ray results were obtained also for GB EX and GB PR (supplementary material – Fig. S10). In Witzleb et al. (2012) the lower drug release from GB matrices was explained by the so called ''blooming effect'' where during storage sharp needle-like glyceride crystals are growing on the unit surface. These crystals are increasing the surface area of the matrix and the contact angle with water making the unit less prone to wettability. It is worth pointing out the interesting difference between the behaviour of stored GB GMT and GB EX units: GMT showed a significantly slower drug release and significantly higher increase in glyceride enthalpy (130.1 J/g) compared to EX (109.5 J/g) after storage at accelerated conditions. These differences may be linked to the high exposure of GB to mechanical stress when GMT are produced (milling, compression) which subsequently may lead into more extensive crystal transformation of the glyceride and thus a larger reduction of drug release.

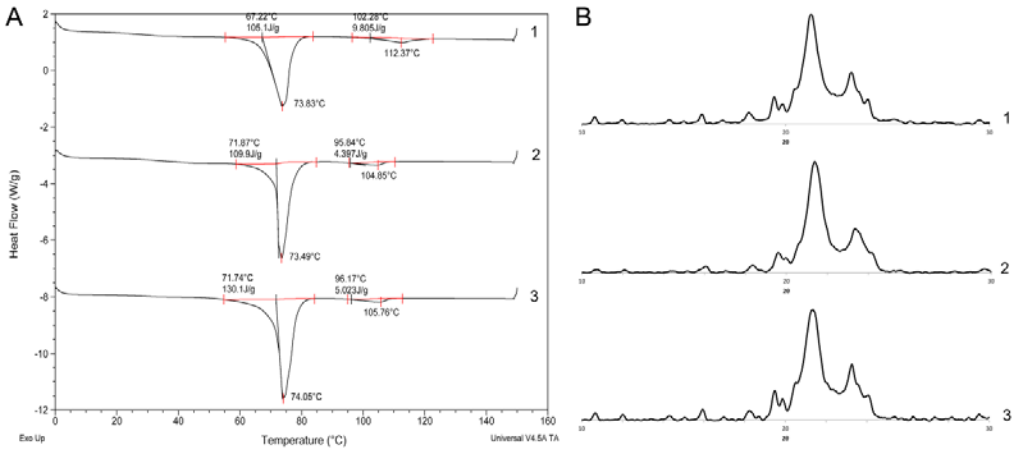

Fig. 10. Influence of storage conditions on the solid state properties of the constituents of GB GMT. (A) Thermograms of GB GMT (1) freshly prepared; (2) stored at room conditions; (3) stored at elevated temperature; (B) X-ray diffractograms of GB GMT (1) freshly prepared (2) stored at room conditions; (3) stored at elevated temperature.

When considering GPS samples, units stored at both room and extreme conditions yielded significantly faster drug release rate compared to the fresh products (Fig. 9B, Table 2 and supplementary material – Fig. S9). Similar results were also seen by Reitz and Kleinebudde (2007a) for theophylline loaded GPS EX stored at 40°C/75% RH. This phenomenon was mostly pronounced in case of extrudates (Fig. 9B) wherein the sigmoid MPT delivery pattern of fresh samples changed towards a square root of time extended release pattern (GPS EX at 40°C (R^2=0.993, RMSD=2.0%)). Changes in drug delivery from GPS units after storage are probably caused by alterations in the glyceride crystal behaviour shown as differences in thermal outcomes and diffractional behaviour (Fig. 11 for GPS EX). DSC studies (Fig. 11A) revealed that storage of GPS EX increased the glyceride enthalpy and melting peak maximum, and changed the peak form. X-ray measurements of stored GPS units (Fig. 11B for GPS EX and supplementary material – Fig. S11 for GPS GMT and GPS PR) revealed changes appearing with time (broadening of main GPS peak at 21.2°) and changes appearing with time and increased temperatures (appearance of triple GPS peak at 19.5°, 21.6° and 23.4°). As pointed by Chauhan et al. (2005) for matrices based on Gelucire 43/01 (containing mainly saturated triglycerides of lauric, stearic and palmitic acid), aging changed the lipid crystallinity which may induce an increase of unit porosity

and subsequently faster drug release [Chauhan et al., 2005]. Obtained results for solid state properties of stored GB and GPS samples are in accordance with previously conducted studies [Hamdani et al., 2003; Reitz and Kleinebudde, 2007a; Reitz and Kleinebudde, 2007c]. Moisture as factor affecting sample solid state behaviour and thus dissolution outcome could be excluded since storage was conducted in heat-sealed aluminium bags with low water vapour permeability.

Results from this section suggest that storage at room conditions (for GPS samples) and especially accelerated conditions (for both GB and GPS samples) affected solid state properties of the used glycerides which can be linked to the observed alterations of drug delivery pattern. Hamdani et al. (2003) state that after thermal treatment of glycerides by (partial) melting they presumably appear as less crystalline layered structures (partial amorphous), which gradually with time and other promoters (increased temperature, mechanical treatment) crystalize into more defined and stable forms. Glycerides with longer fatty acid chain (GB, behenic acid C22) are more resistant to changes and require more time and more severe conditions compared to glycerides with shorter fatty acid chains (GPS, palmitic acid C16 and stearic acid C18) [Hamdani et al., 2003]. MPT shows its x-ray peaks at their native positions which outlines stability of its polymorphic form also during storage.

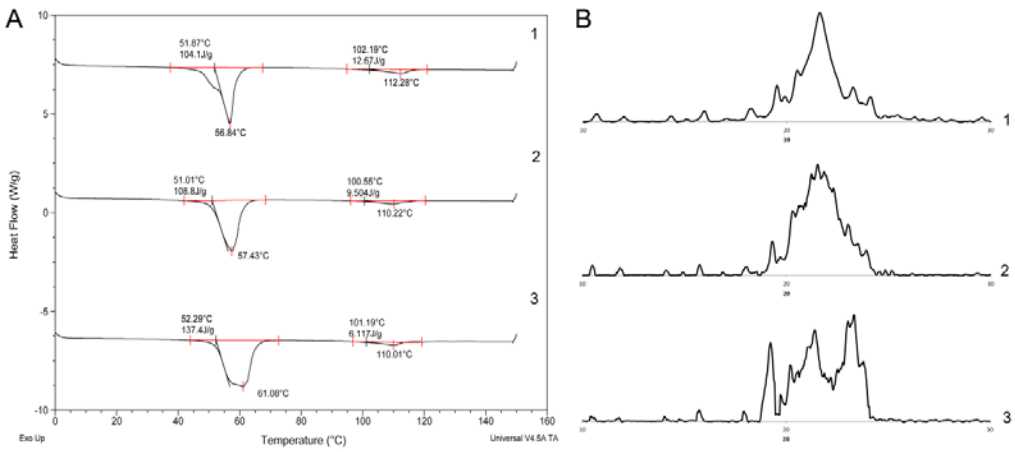

Fig. 11. Influence of storage conditions on the solid state properties of the constituents of GPS EX. (A) Thermograms of GPS EX (1) freshly prepared; (2) stored at room conditions; (3) stored at elevated temperature; (B) X-ray diffractograms of GPS EX (1) freshly prepared (2) stored at room conditions; (3) stored at elevated temperature.

3.4 Effect of the media's composition on the drug release pattern from different glyceride matrices

By submitting GB-based units to dissolution testing in 0.1 N HCl (pH 1) and phosphate buffer with pH 6.8 (PB) there were no significant differences in the drug release profile in these two media. The results of the dissolution studies of GB GMT units in different media are given in Fig. 12A and Table 2. On the other hand all matrices containing GPS as release retarding agent showed slightly faster drug release in PB compared to 0.1 M HCl (Fig. 12B and Table 2 for GPS GMT). The reason for this behaviour may be due to the partial ionization of the functional groups of the free fatty acids present in GPS (acid value ≤ 6mg KOH/g [Technical data sheet – PRECIROL ATO 5]) in PB pH which decreased the hydrophobicity of the system and enhanced the release rate [Vervaeck et al., 2013]. Lower acid value of GB (≤ 4mg KOH/g [Technical data sheet – COMPRITOL 888 ATO]) could be a factor limiting the influence of the PB pH on the hydrophobicity of the matrix and drug delivery changes by pH variation.

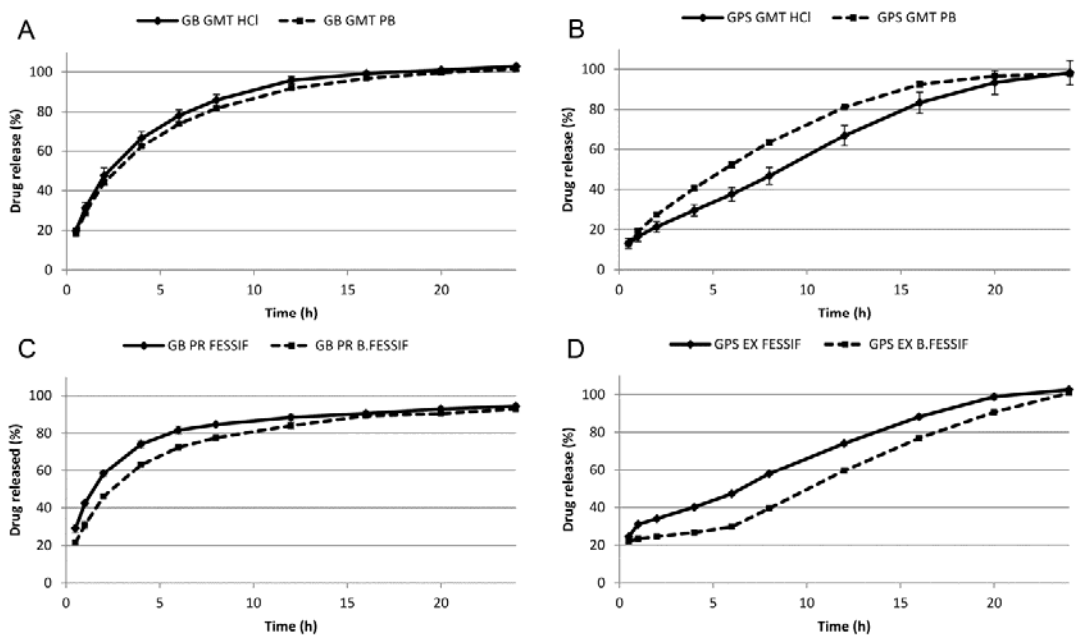

Fig. 12 – Effects of dissolution medium properties/composition on drug release of GB based matrices. Influence of medium's pH on MPT from (A) GB GMT; (B) GPS GMT (HCl – pH = 1, PB – phosphate buffer with pH=6.8); FESSIF medium composition on MPT release from (C) GB PR and (D) GPS EX (FESSIF – composition with pancreatin, B.FESSIF – blank FESSIF).

Glycerides are one of the main constituents of everyday human nutrition. Their presence in the gastrointestinal tract (GIT) stimulates secretion of pancreatic juice (containing among others enzyme lipase) and bile (rich in bile salts and phospholipids). Lipase causes di- and triglycerides digestion to monoglycerides and free fatty acids (lipolysis). Digested products are further solubilized by phospholipids and bile salts and as such absorbed [Witzleb et al., 2012]. Dissolution studies in FESSIF and blank FESSIF were performed in order to simulate GIT digestion of formulated glycerides and predict the influence of biorelevant media constituents (especially lipase) on the MPT delivery.

GPS EX tested in modified FESSIF medium containing pancreatin, CaCl2, bile salts and phospholipids gave faster MPT delivery compared to samples tested in blank-FESSIF (Fig. 12 D and Table 2 for GPS EX). GPS GMT and PR were affected in a similar but less extensive manner (supplementary material – Fig. S12). MPT release from EX and GMT based on GB was not

significantly affected by the biorelevant medium (supplementary material – Fig. S12) as was also reported also by Witzleb et al. (2012). On the other hand in case of GB PR, drug delivery was only slightly faster in FESSIF compared to blank FESSIF (Fig. 12C and Table 2), possibly due to the large surface area and central void/crack of prills exposed to biorelevant medium, which is able to affect the structure of the glyceride. Results indicated that GPS as glyceride is in general more affected by biorelevant medium compared to GB. This finding is in accordance with the ones of Witzleb et al. (2012) and Bolko et al. (2014) stating that glycerides composed of shorter fatty acid chains (in our case GPS - palmitic acid C16 and stearic acid C18) are more affected by biorelevant media (mainly by lipolysis) compared to glycerides composed of longer fatty acid chains (in our case GB - behenic acid C22).

4. CONCLUSIONS

Within this research we have developed sustained release MDDS based on GB and GPS as matrix formers and MPT as model drug. MDDS mini-matrices were produced by three different technologies: hot-melt extrusion, tableting (after granulation) and prilling. While the first two methods were seen as robust and reproducible ones prilling turned out to be susceptible to high viscosities and was feasible only at lowest drug amount (20%). Independent of glyceride and process type drug dissolution was affected by drug loading, unit size and storage under elevated temperature. Dissolution profile changes induced by storage at elevated temperature were associated with detected changes in the crystalline properties of the lipid. GPS as carrier gave matrices with lower porosity compared with the ones based on GB and thus in general exhibited slower drug release when compared to the GB based matrices. However due to the diverse release pattern of differently produced GPS matrices, followed by their instability after storage at room conditions and susceptibility to dissolution medium composition, GPS was seen as less robust and reliable matrix former when compared to GB. Drug release patterns of GB based matrices proved to be unaffected by the production type, dissolution conditions and storage for two months at room temperatures.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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